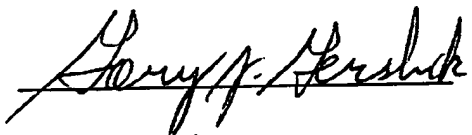
No fee is deemed necessary in connection with the filing of this Supplemental Amendment and Supplemental Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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WO 01/34574 A1

(54) Title: STABLE POLYMORPH OF N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE, METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

(57) Abstract: The present invention relates to a stable crystalline form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph, its production in essentially pure form, and its use. The invention also relates to the pharmaceutical compositions containing the stable polymorph B form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine as hydrochloride, as well as other forms of the compound, and to methods of treating hyperproliferative disorders, such as cancer, by administering the compound.

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
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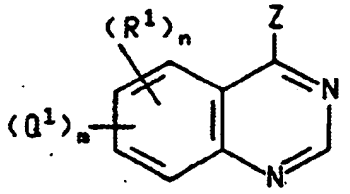
(54) 4-Aminoquinazoline derivatives

(57) This invention relates to certain 4-aminoquinazoline derivatives of the formula



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and their pharmaceutically acceptable salts wherein R^1, Q^1, m, n, and Z are defined as in the specification. The compounds of formula I and pharmaceutically acceptable salts are useful for the treatment of hyperproliferative disorders and conditions in mammals.

EP 0 837 063 A1

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PRODUCTION OF AMINOPHENYLACETYLENE COMPOUND

Patent Number: JP10036325
Publication date: 1998-02-10
Inventor(s): YAMAKAWA KAZUYOSHI; SATO TADAHISA
Applicant(s): FUJI PHOTO FILM CO LTD
Requested Patent: JP10036325
Application Number: JP19960207786 19960718
Priority Number(s):
IPC Classification: C07C211/45; C07C209/36; C07C213/02; C07C215/68; C07C215/70; C07F7/10
EC Classification:
Equivalents:

Abstract

PROBLEM TO BE SOLVED: To enable to effectively obtain the subject compound useful as an intermediate for synthesizing antifogging agents for heat-developable photosensitizing materials, etc., at a low cost by selectively reducing a nitrophenylacetylene compound with iron (compound).
SOLUTION: This method for producing an aminophenylacetylene compound of formula II comprises selectively reducing (A) a compound of formula I [R<1> is H, a group of the formula: CR<2> R<3> OH (R<2> , R<3> are each H, an alkyl, or R<2> and R<3> may be combined with each other to form a five to seven-membered ring), a group of the formula: SiR<4> R<5> R<6> (R<4> to R<6> are each an alkyl)] with (B) iron (salt) (e.g. iron powder or reduced iron activated with acetic acid, hydrochloric acid, ammonium chloride or a nickel chloride, the mixture of ferric trichloride with a hydrogen-donor such as a hydrazine compound, ferrous dichloride of ferric trichloride). The reaction is preferably carried out by reacting 1 equivalent of the component A with 0.1-10 equivalents of the component B at a temperature of 0-150 deg.C.

ACID ADDUCT SALT OF 3-ETHYNYLANILINE COMPOUND AND PURIFICATION OF 3-ETHYNYLANILINE COMPOUND

Patent Number: JP10036326
Publication date: 1998-02-10

Inventor(s): YAMAKAWA KAZUYOSHI; SATO TADAHISA
Applicant(s): FUJI PHOTO FILM CO LTD

Requested Patent: ☐ JP10036326
Application Number: JP19960207787 19960718
Priority Number(s):
IPC Classification: C07C211/46; C07C209/84
EC Classification:
Equivalents:

Abstract

PROBLEM TO BE SOLVED: To obtain the subject new acid adduct salt having the form of a specific acid adduct salt, capable of being easily crystallized for its purification, excellent in storage stability and useful as an intermediate for synthesizing thermosetting resins, nonlinear optical materials, etc.
SOLUTION: A compound of formula I [X<-> is BF4 <-> , PF6 <-> , ClO4 <-> , a halogen ion, a group of formula II (R<1> is OH, an alkyl, an aryl), a group of formula III (Z is a single bond, methylene, ethylene, phenylene)]. For example, 3-ethynylaniline sulfuric acid salt. The compound of formula I is obtained by dissolving a 3-ethynylaniline compound in an organic solvent (preferably an aromatic hydrocarbon solvent, an aliphatic hydrocarbon solvent, an ester solvent), adding an acid of the formula: HX to the solution and subsequently filtering off the deposited crystals.

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Exhibit 12

QUINAZOLINE DERIVATIVE

Patent Number: EP0726267

Publication date: 1996-08-14

Inventor(s): MORIYAMA TAKAHIRO (JP); NONAKA HIROMI (JP); KARASAWA AKIRA (JP); OKAMURA YUKO (JP); TAKAI HARUKI (JP); YAO KOZO (JP); FUJIWARA SHIGEKI (JP)

Applicant(s): KYOWA HAKKO KOGYO KK (JP)

Requested Patent: EP0726267, A4, B1

Application Number: EP19950929231 19950825

Priority Number (s): WO1995JP01694 19950825; JP19940202018 19940826

IPC Classification: C07D401/14; A61K31/55; A61K31/505

EC Classification: C07D401/14, C07D401/14R

Equivalents: AU3265595, AU689304, CA2174854, CN1043991B, CN1134150, DE69519469D, DE69519469T, ES2153491T, FI961758, JP9165385, NO310658B, NO961601, NZ291506, US5948784, WO9606841

Cited Documents:

Abstract

Disclosed are quinazoline derivatives represented by formula (I): wherein R<1> represents hydrogen, lower alkyl, alkenyl, or aralkyl; R<2>, R<3>, R<4>, and R<5> represent hydrogen, lower alkyl, lower alkoxy, lower alkanoyl, or the like; R<6>, R<7>, R<8>, and R<9> represent hydrogen, lower alkyl, lower alkoxy, aralkyloxy, or the like, or any adjoining two of them are combined to form methylenedioxy or the like; R<10> represents hydrogen, lower alkyl, or the like; R<11> and R<12> represent hydrogen, lower alkyl, cycloalkyl, phenyl, or aralkyl, or R<11> and R<12> are combined together with N to form a heterocyclic group; and n represents 0, 1 or 2, and pharmaceutically acceptable salts thereof. These compounds have adenosine uptake inhibitory activity and are useful for the protection of myocardium and for the prevention or treatment of inflammation such as leg and foot edema.

Quinazoline derivatives.

Patent Number: EP0566226, B1

Publication date: 1993-10-20

Inventor(s): BARKER ANDREW JOHN (GB)

Applicant(s): ZENECA LTD (GB)

Requested Patent: RU2127263

Application Number: EP19930300270 19930115

Priority Number (s): GB19920001095 19920120; GB19920013572 19920626; GB19920023735 19921112

IPC Classification: C07D239/94; C07D491/056; C07D403/12; A61K31/505

EC Classification: C07D239/94, C07D403/04, C07D491/04

Equivalents: AU3101093, AU661533, CA2086968, CZ9300043, DE69300754D, DE69300754T, ES2078798T, FI930208, HK36497, HU63153, HU9500185, IL104479, KR229294, NO301541B, NO930178, NZ245662, SK1693

Cited Documents: GB2160201; US3985749; GB2033894; WO9214716; EP0520722

Abstract

The invention concerns quinazoline derivatives of the formula I wherein m is 1, 2 or 3 and each R<1> includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl] carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C) alkoxy and (1-3C)alkylenedioxy; n is 1 or 2 and each R<2> includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically-acceptable salt thereof; processes for their preparation; pharmaceutical compositions containing them; and the use of the receptor tyrosine kinase inhibitory properties of the compounds in the treatment of cancer.

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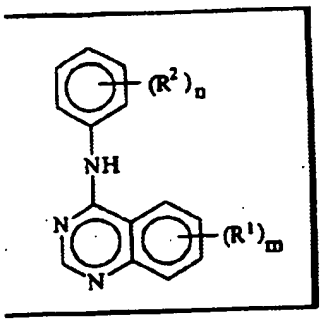
7) Described are the compounds



nd pharmaceutically acceptable salts thereof, which are useful in the treatment of cancer.

a these compounds,

n is 1, 2 or 3;

i is 1 or 2; each

R^1 is independently OH, amino, substituted amino, carboxy, ureido, 3-phenylureido, carbamoyl, C_{1-4}-alkoxycarbonyl, N-C_{1-4}-alkylcarbamoyl, N,N-di-C_{1-4}-alkylcarbamoyl, OCF_3 optionally substituted C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, optionally substituted C_{1-4}-alkyl, C_{2-4}-alkanoyloxy, hydroxy-C_{2-6}-alkanoyloxy, C_{1-4}-alkoxy-C_{2-4}-alkanoyloxy, substituted C_{1-4}-alkylamino, optionally substituted benzamido, optionally substituted benzenesulphonamido, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4}-alkylpiperazin-1-yl, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl, or two R^1 groups together form a C_{1-3}-alkylenedioxy group; and each R^2 is independently H, OH, CF_3, halo, amino, NO_2, CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, mono- or di-C_{1-4}-alkylamino, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{2-4}-alkanoylamino, optionally substituted benzamido or C_{2-4}-alkanoyl.

D2

A Simple and Economical Synthetic Route to *p*-Ethynylaniline and Ethynyl-Terminated Substrates

Anastasios P. Melissaris† and Morton H. Litt*

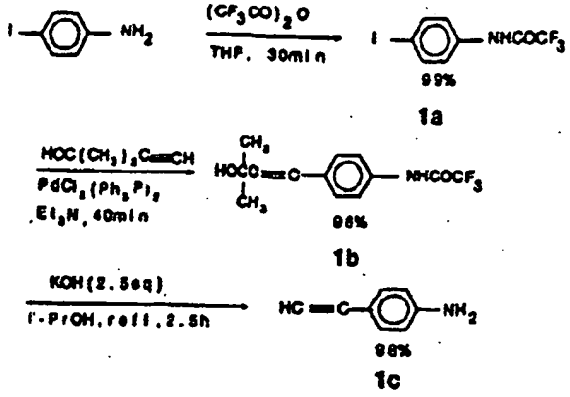
Department of Macromolecular Science, Case Western Reserve University, Cleveland, Ohio 44106

Received July 12, 1993 (Revised Manuscript Received June 20, 1994)

Introduction

Acetylenic compounds have been used for the synthesis of high performance polymers and for systems which exhibit nonlinear optical properties. Classical methods for the synthesis of terminal arylacetylenes in general involve manipulation of preformed, two-carbon side chains and include methods such as the Vilsmeier method[1-3] or the halogenation–dehydrohalogenation sequence of vinyl aromatics[4] and ketones.[5,6] An innovation in the synthesis of arylacetylenic compounds has been to use protecting groups.[7] Acetylene, protected at one end, can be added to an aromatic nucleus via coupling at the free end. Subsequent removal of the protecting group generates a terminal arylacetylene. The widely accepted procedure for the addition of an acetylenic substituent to an aromatic nucleus is the Stephens–Castro coupling reaction[8-10] between an aryl iodide and a protected acetylide in pyridine at reflux. More recent advances in the synthesis of arylacetylenes[11,12] use a two-step route; the first step involves the coupling of an aryl iodide with (trimethylsilyl)acetylene (TMSA) in the presence of Pd(0)/Cu(I) in pyridine. The second step is removal of the protecting group (trimethylsilyl) to yield the arylacetylene. The trimethylsilyl protecting group is easily removed by treatment with dilute potassium hydroxide or potassium carbonate. However, because of the prohibitively high cost of the TMSA, this route has been limited to small-scale preparations. There has been a great interest in the development of methods for introducing an ethynyl group[13-18] into organic structures.

Scheme 1. Synthetic Route to *p*-Ethynylaniline



For the synthesis of *p*-ethynylaniline (1c) (Scheme 1), four methods[13,16-18] have been reported. The yields vary from poor to moderate (30–65%) and the reactions are cumbersome and costly to perform on a large scale. The most interesting procedure for the synthesis of 1c[11] entails coupling of *p*-iodoaniline with (trimethylsilyl)-acetylene (TMSA) in the presence of a palladium complex and a copper(I) salt. Due to the high cost of TMSA, this route for all practical purposes has been limited to small-scale procedures.[19-23] J. Stille and T. Takeichi[17] synthesized 1c using (tributylstannyl)acetylene (TBSA) and *p*-iodoaniline in 30% overall yield.

Attempts to synthesize larger quantities of 1c using inexpensive reagents have been unsuccessful up to date. 2-Methyl-3-butyn-2-ol (MEBYNOL) has been used by other investigators to synthesize 1c because of its very low cost. Bardamova et al.[15] synthesized 1c on a milligram scale by direct coupling of *p*-iodoaniline with MEBYNOL, followed by deprotection and heating the intermediate 4-anilino-2-methyl-3-butyn-2-ol under a high vacuum in the presence of well-ground KOH and catalytic amounts of hydroquinone. However, most of the desired product decomposed under these severe conditions. Takalo et al.[16] reported a modified procedure for deprotecting 4-anilino-2-methyl-3-butyn-2-ol, heating under distillation conditions in the presence of NaOH pellets in toluene for 2 h. 1c was synthesized in 30% overall yield. The methods of Bardamova[15] and Takalo[16] have not been used for the synthesis of 1c because the yields were low and some decomposition products were generated during the deprotection step.

Due to the high cost of TMSA, we decided to develop a simple high yield route to 1c using the very inexpensive reagent MEBYNOL. We have reported a new synthesis of *p*-ethynylbenzoic acid and p-ethynyl benzoyl chloride, using MEBYNOL.[14] We now report an economical and efficient synthesis of 1c using a modified route which is simpler and less expensive than the methods previously reported. This method gives an almost quantitative yield of high purity product. The low yields and the various

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D2

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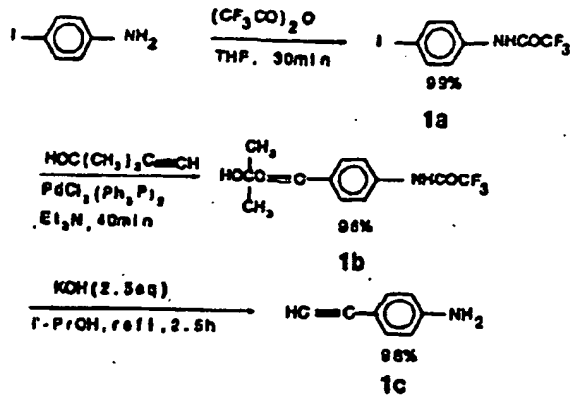

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who, after being duly sworn, deposes and states: Elisabeth A. Lucas

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That he is thoroughly conversant with these languages;

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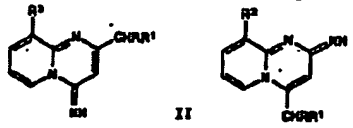
THIS SEP 16 2003

Susan Tapley
Notary Public, State of New York
No. 01TA4999804
Qualified in Queens County
Certificate filed in New York County
and Kings County
Commission Expires July 27, 2006

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Exhibit 18

was prepd. in 5 steps from 6-methyl-5-nitroindazole. Key intermediate was the aminoindazolecarboxylic acid III, which was annulated by heating at 70° with HC(:NH)NH$_2$.AcOH for 2 days to give 91% II. I (RR^1 = O, R^2 = H) was prepd. in 76% yield from III by fusion with (H$_2$N)$_2$CO at 160° for 15 min. Pyrazoloquinazolinedione IV was prepd. in 35% overall yield from 5,2-Me(HO$_2$C)C$_6$H$_3$NHAc in 8 steps and pyrazoloquinazolinone V was prepd., in 5 steps, from 5-methyl-4-nitroindazole.

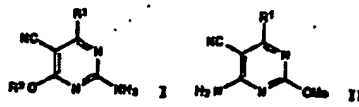
96: 122723r **Synthesis of 2- and 4-iminopyrido[1,2-a]pyrimidines from allenic nitriles and 2-aminopyridines.** Fomum, Z. Tanee; Mbafor, J. Tanyi; Landor, Phyllis D.; Landor, Stephen R. (Univ. Yaounde, Yaounde, Cameroon). *Tetrahedron Lett.* 1981, 22(41), 4127–8 (Eng). Heating RCR^1:C:CHCN (I; R



II III

= Me, R^1 = Et, Pr; R = R^1 = Et) under reflux with 2-amino- or 2,3-diaminopyridine in alc. soln. for 48 h gave 87–94% 4-iminopyridopyrimidine II (R, R^1 as before, R^2 = H, NH$_2$, resp.), whereas similar treatment of I (R = R^1 = Me; R = Pr, R^1 = H) with 2-aminopyridine and I (R = Me, Et, R^1 = Et) with 3-hydroxy-2-aminopyridine gave 90–2% 2-iminopyridopyrimidine III (R, R^1 as before, R^2 = H, OH, resp.).

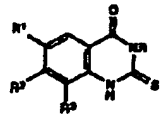
96: 122724s **Synthesis of 6-alkoxy-2-amino-5-cyanopyrimidines through sodium alkoxide-induced regiospecific cyclization of 1,3-dicarbonitriles.** Perez, Miguel A.; Soto, Jose L. (Fac. Quim., Univ. Complutense, Madrid, Spain). *Synthesis* 1981, (12), 955–8 (Eng). The reaction of R^{1}C(OR):C(CN)$_2$



I II

(R = Et, Me; R^1 = H, Me, Ph, tolyl, anisyl, ClC$_6$H$_4$, O$_2$NC$_6$H$_4$) with H$_2$NCN and NaOR^2–R^{2}OH (R^2 = Me, Et, Pr) yielded the resp. pyrimidinecarbonitriles I. Similarly, pyrimidines II were prepd. from R^{1}C(OR):C(CN)$_2$, H$_2$NC(OMe):N$^+$H$_2$ Cl$^-$, and NaOMe–MeOH. A mixt. of EtOCH:C(CN)$_2$, H$_2$NCH, and NaOMe in MeOH was refluxed to give I (R^1 = H, R^2 = Me).

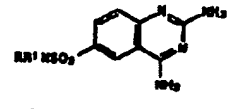
96: 122725t **Preparation of 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines from methyl N-aryldithiocarbamates and anthranilic acid.** Mayoral, J.; Melendez, E.; Merchan, P.; Sanchez, J. (Dep. Quim. Org., Univ. Zaragoza, Zaragoza, Spain). *Synthesis* 1981, (12), 962 (Eng). The cyclocondensation



I

reaction of RNHCS$_2$Me (R = tolyl, xylyl, methylchlorophenyl, (methylenedioxy)phenyl (trifluoromethyl)phenyl, Ph, anisyl] with anthranilic acids gave the resp. quinazolinonethiones I (R^1 = H, Cl; R^2 = H, NO$_2$, Cl; R^3 = H, Cl). Thus, 4-MeC$_6$H$_4$NHCS$_2$Me in DMF was added dropwise to 2-H$_2$NC$_6$H$_4$CO$_2$H in DMF at room temp., and the mixt. was refluxed to give I (R = 4-MeC$_6$H$_4$, R^1 = R^2 = R^3 = H).

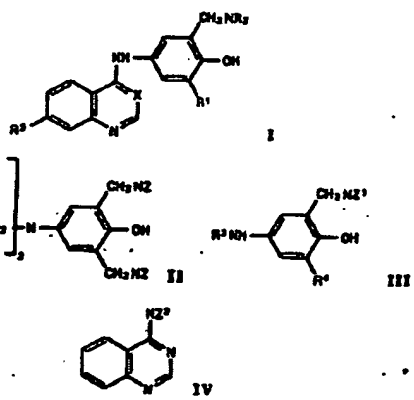
96: 122726u **Studies on antimalarial agents. VI. Synthesis and their antimalarial activities of 2,4-diamino-6-substituted-aminosulfonylquinazoline derivatives.** Zhang, Xiuping; Shen, Defu; Zhang, Xiuju; Chen, Lin; Dai, Zurui; Shu, Kangquan (Shanghai Inst. Pharm. Ind. Res., Shanghai, Peop. Rep. China). *Yaoxue Xuebao* 1981, 16(11), 877–80 (Ch).



I

Sixteen quinazolinesulfonamides I [NRR^1 = alkylamino, 1-pyrrolidinyl, piperidino (II), morpholino, etc.] were prepd. by amidation of 2,4-diaminoquinazoline-6-sulfonyl chloride. II showed pronounced prophylactic activity against *Plasmodium yoelii*.

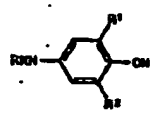
96: 122727v **Studies on drugs for coronary diseases. II. Synthesis of compounds related to changrolin, a new antiarrhythmic agent.** Sun, Cunji; Zhang, Xinyi; Yang, Xingzhong; Wang, Pingping; Shen, Jian; Shu, Yun; Ji, Ruyun; Kyi, Zuyoong (Shanghai Inst. Mater. Med., Acad. Sin., Shanghai, Peop. Rep. China). *Yaoxue Xuebao* 1981, 16(8), 564–70 (Ch). Changrolin (I; NR$_2$ = 1-pyrrolidinyl, R^1 = 1-pyrrolidinylmethyl, R^2 = H, X = N) analogs, i.e., I [NR$_2$ = NMe$_2$, N(CH$_2$CH$_2$OH)$_2$, morpholino, etc; R^1 = H, CH$_2$NR$_2$; R^2 = H; X = N], I (NR$_2$ = NMe$_2$, 1-pyrrolidinyl; R^1 = H, CH$_2$NR$_2$; R^2 = Cl; X = CH), II



I II III IV

(NZ = NMe$_2$, 1-pyrrolidinyl, 1-piperidinyl, morpholino), III (NZ^1 = NMe$_2$, 1-pyrrolidinyl, morpholino, etc.; R^3 = Ac, Bz; R^4 = H, CH$_2$NZ^1) and IV (NZ^2 = NMe$_2$, 1-pyrrolidinyl, morpholino, etc.) were prepd. by known reactions. III (NZ^1 = 1-pyrrolidinyl, R^3 = Bz, R^4 = CH$_2$NZ^1) was more effective than changrolin in protecting dogs from arterial fibrillation.

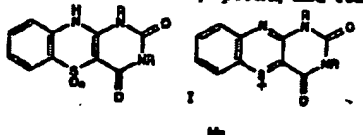
96: 122728w **Studies on antiarrhythmics - synthesis of 2-[(alkylamino)methyl]- and 2,6-bis[(alkylamino)methyl]-4-(substituted amino)phenols.** Lin, Mulan; Liu, Yufang; Lu, Yongyu; Zhang, Huiqin; Zheng, Weimin (Tianjin Inst. Pharm. Ind. Res., Tianjin, Peop. Rep. China). *Yaoxue Xuebao* 1981, 16(10), 757–61 (Ch). 4-Aminophenols I [R = Ac, 2,6-diamino(or



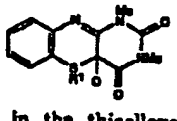
I

dimethyl)-4-pyrimidinyl, 1-phthalazinyl, 6,7-dimethoxy-4-quinazolinyl, etc.; R^1, R^2 = H, Et$_2$NCH$_2$, 1-pyrrolidinylmethyl, piperidinomethyl, morpholinomethyl] (37 compds.) were prepd. by known reactions. Some I showed antiarrhythmic activity.

96: 122729x **Redox reactions of 10H-pyrimido[5,4-b][1,4]benzothiazines.** Fenner, Helmut; Roessler, Hellmuth H.; Grauert, Rolf W. (Inst. Pharm., Freien Univ., D-1000 Berlin, 33 Fed. Rep. Ger.). *Arch. Pharm. (Weinheim, Ger.)* 1981, 314(12), 1023–30 (Ger). The structure, spectra, and reactivity of mcl.



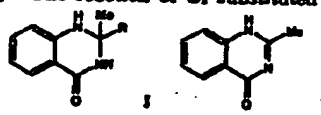
I II



III

species participating in the thiaalloxazine redox system are described. Oxidn. of I (R = H, Me, *n* = 0) gave the cations II which were hydrolyzed to I (*n* = 1) or alcoholyzed to III (R^1 = H, Me, Et, Pr, CHMe$_2$, Bu).

96: 122730r **Reaction of 1,2,3,4-tetrahydroquinazolin-4-ones with acid anhydride. III.** Yamato, Masatoshi; Horiuchi, Jiroh; Takeuchi, Yasuo (Fac. Pharm. Sci., Okayama Univ., Okayama, Japan 700). *Chem. Pharm. Bull.* 1981, 29(11), 3124–9 (Eng). The reaction of C$_2$-substituted 1,2,3,4-tetrahydroquinazolin-4-ones with Ac$_2$O and pyridine was carried out in order to elucidate the effect of the C$_2$-substituent. It was found that the various types of reactions occurred depending on the kind and no. of C$_2$-substituents of 1,2,3,4-tetrahydroquinazolin-4-ones. Thus, the quinazolinone I (R = PhCH$_2$CH$_2$) was treated with Ac$_2$O at 100° for 3 h to give the quinazolinone II (21%). I (R = Ph) reacted with Ac$_2$O to give 68% *o*-(PhCMe:N)C$_6$H$_4$CONHAc.



I II

96: 122731s **Studies on fluorinated pyrimidines. I. A new method of synthesizing 5-fluorouracil and its derivatives.** Miyashita, Osamu; Matsumura, Koichi; Shimadzu, Hiroshi; Hashimoto, Naoto (Cent. Res. Div., Takeda Chem. Ind., Ltd., Osaka, Japan 532). *Chem. Pharm. Bull.* 1981, 29(11), 3181–90 (Eng). Title compds. I (R = H, R^1 = F, R^2 = CO$_2$Me, R^3 = H,

134a Tetrahedron Letters
36(1995) August 14, No. 33, Kidlington, Oxford, GB

Pergamon

Tetrahedron Letters, Vol. 36, No. 33, pp. 5891-5894, 1995
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0040-4039(95)01172-2

C07D 317/72C

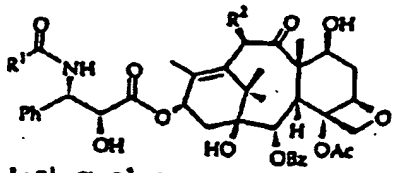
A Convergent Synthesis of Functionalized *B-seco* Taxane Skeletons

Christian Montalbetti, Monique Savignac, Félicie Bonnefis and Jean Pierre Genêt.

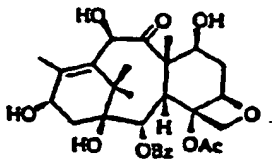
Laboratoire de Synthèse Organique, associé au CNRS, Ecole Nationale Supérieure de Chimie de Paris.
11 rue Pierre et Marie Curie - 75231 Paris Cedex 05 - France

Abstract : The sequential Sonogashira cross-coupling reactions with water soluble and anhydrous Pd(0) catalysts between vinylic iodo derivatives **6**, **8** and 3-iodocyclohexenone **7** with trimethyl silyl acetylene are used to produce functionalized intermediates **11** and **18**. Conjugate addition followed by enolate trapping with trimethyl orthoformate provided B-*seco* taxane derivatives **14** and **20**.

The antitumor agents, paclitaxel (Taxol®) **1** and docetaxel (Taxotere®) **2** have generated much excitement due to their activities against advanced ovarian and breast cancer.[1] Taxol **1** has been the subject of extensive chemical and biological studies, which have been summarized in recent reviews.[1c,2] The recent total syntheses of taxol accomplished by Nicolaou[3] and Holton[4] are seminal achievements in the field.

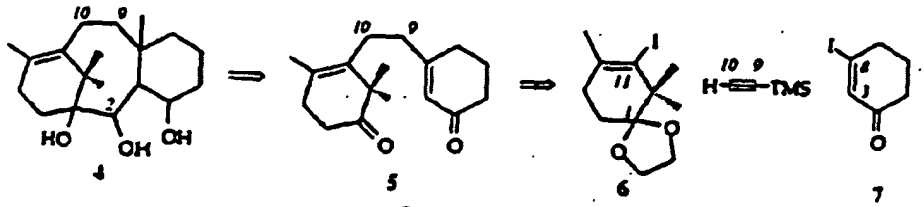


1 : R^1 = Ph R^2 = OAc
2 : R^1 = OtBu R^2 = OH



3

The challenge now is to provide new methodologies for the synthesis of 10-deacetylbaccatin III **3** [2b] analogues[5] which can rapidly lead to the analogues of taxol and taxotere.



4 **5** **6** **7**

Scheme 1

We wish to report a convergent synthesis of B-*seco* taxane precursors of taxoids **4** by linking the future A and C rings through a two carbon moiety, via a sequential Sonogashira[6] reaction between the protected iodo-ketone **6** and 3-iodocyclohexenone **7** (Scheme 1).

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SEP 11 2006

Susan Tapley

Susan Tapley
Notary Public, State of New York
No. 01TA4999804
Qualified in Queens County
Certificate filed in New York County and Kings County
Commission Expires July 27, 2006

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Exhibit 10

QUINAZOLINE DERIVATIVE

Patent Number: EP0726267
Publication date: 1996-08-14
Inventor(s): MORIYAMA TAKAHIRO (JP); NONAKA HIROMI (JP); KARASAWA AKIRA (JP); OKAMURA YUKO (JP); TAKAI HARUKI (JP); YAO KOZO (JP); FUJIWARA SHIGEKI (JP)
Applicant(s): KYOWA HAKKO KOGYO KK (JP)
Requested Patent: EP0726267, A4, B1
Application Number: EP19950929231 19950825
Priority Number (s): WO1995JP01694 19950825; JP19940202018 19940826
IPC Classification: C07D401/14; A61K31/55; A61K31/505
EC Classification: C07D401/14, C07D401/14R
Equivalents: AU3265595, AU689304, CA2174854, CN1043991B, CN1134150, DE69519469D, DE69519469T, ES2153491T, FI961758, JP9165385, NO310658B, NO961601, NZ291506, US5948784, WO9606841
Cited Documents:

Abstract

Disclosed are quinazoline derivatives represented by formula (I): wherein R<1> represents hydrogen, lower alkyl, alkenyl, or aralkyl; R<2>, R<3>, R<4>, and R<5> represent hydrogen, lower alkyl, lower alkoxy, lower alkanoyl, or the like; R<6>, R<7>, R<8>, and R<9> represent hydrogen, lower alkyl, lower alkoxy, aralkyloxy, or the like, or any adjoining two of them are combined to form methylenedioxy or the like; R<10> represents hydrogen, lower alkyl, or the like; R<11> and R<12> represent hydrogen, lower alkyl, cycloalkyl, phenyl, or aralkyl, or R<11> and R<12> are combined together with N to form a heterocyclic group; and n represents 0, 1 or 2, and pharmaceutically acceptable salts thereof. These compounds have adenosine uptake inhibitory activity and are useful for the protection of myocardium and for the prevention or treatment of inflammation such as leg and foot edema.

EP0566226 Biblio Desc Claims Page 1

esp@cenet

Quinazoline derivatives.

Patent Number: EP0566226, B1

Publication date: 1993-10-20

Inventor(s): BARKER ANDREW JOHN (GB)

Applicant(s): ZENECA LTD (GB)

Requested Patent: RU2127263

Application Number: EP19930300270 19930115

Priority Number (s): GB19920001095 19920120; GB19920013572 19920626; GB19920023735 19921112

IPC Classification: C07D239/94; C07D491/056; C07D403/12; A61K31/505

EC Classification: C07D239/94, C07D403/04, C07D491/04

Equivalents: AU3101093, AU661533, CA2086968, CZ9300043, DE69300754D, DE69300754T, ES2078798T, FI930208, HK36497, HU63153, HU9500185, IL104479, KR229294, NO301541B, NO930178, NZ245662, SK1693

Cited Documents: GB2160201; US3985749; GB2033894; WO9214716; EP0520722

Abstract

The invention concerns quinazoline derivatives of the formula I wherein m is 1, 2 or 3 and each R<1> includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl] carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C) alkoxy and (1-3C)alkylenedioxy; n is 1 or 2 and each R<2> includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically-acceptable salt thereof; processes for their preparation; pharmaceutical compositions containing them; and the use of the receptor tyrosine kinase inhibitory properties of the compounds in the treatment of cancer.

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Exhibit 14

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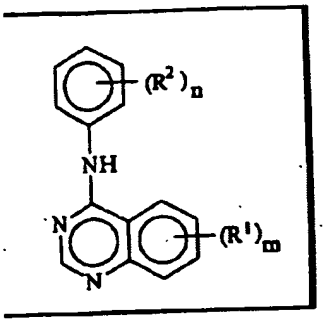
7) Described are the compounds



nd pharmaceutically acceptable salts thereof, which are useful in the treatment of cancer.

ı these compounds,

ı is 1, 2 or 3;

ı is 1 or 2; each

R^1 is independently OH, amino, substituted amino, carboxy, ureido, 3-phenylureido, carbamoyl, C_{1-4}-alkoxycarbonyl, N-C_{1-4}-alkylcarbamoyl, N,N-di-C_{1-4}-alkylcarbamoyl, OCF_3 optionally substituted C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, optionally substituted C_{1-4}-alkyl, C_{2-4}-alkanoyloxy, hydroxy-C_{2-6}-alkanoyloxy, C_{1-4}-alkoxy-C_{2-4}-alkanoyloxy, substituted C_{1-4}-alkylamino, optionally substituted benzamido, optionally substituted benzenesulphonamido, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4}-alkylpiperazin-1-yl, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl, or two R^1 groups together form a C_{1-3}-alkylenedioxy group; and each R^2 is independently H, OH, CF_3, halo, amino, NO_2, CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, mono- or di-C_{1-4}-alkylamino, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{2-4}-alkanoylamino, optionally substituted benzamido or C_{2-4}-alkanoyl.

Applicants: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Exhibit 15